Remarks

Claims 37-40 and 42-46 are pending in this application. The specification has been amended by deleting the prior sequence listing and inserting the new sequence listing. Claim 38 has been amended to correct typographical errors. No new matter is added with these amendments. These amendments are made without prejudice or disclaimer. Applicants reserve the right to prosecute any cancelled or otherwise unclaimed subject matter in this or a separate application, as appropriate. Consideration and entry of these remarks and amendments is respectfully requested.

A. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-7, 11-17, 20, 22, 24-27 and 29 stand rejected under 35 U.S.C. 112, first paragraph. The Examiner alleges that the specification, while being enabling for recombinant monomeric MHC or HLA Class I molecules, does not reasonably provide enablement for recombinant MHC or HLA Class II molecules. Applicants respectfully disagree and traverse these rejections as indicated below.

The Examiner alleges that at the time of invention the synthesis of class II monomers was not well known in the art and points to Barnardo (Transplantation, Vol. 70, No. 3, pp. 531-536, Aug. 15, 2000) to support this allegation. The Examiner also cites U.S. Pat. No. 6,727,070 as disclosing general difficulties associated with protein expression and Frayser et al. (Protein Expression and Purification, 15, pp. 105-114, 1999) and Armilli et al. (J. Biol. Chem., Vol. 270, No. 2, pp. 971-977 (1995)) as disclosing difficulties associated with expressing recombinant class II molecules. As such, the Examiner alleges, one of skill in the art would have had a low level of predictability in making the claimed MHC Class II monomers.

In supporting the allegation of non-enablement, the Examiner cites the Barnardo, Thomas, Frayser and Arimilli references. As shown below in the discussion of Frayser and Arimilli, the synthesis of class II monomers had been accomplished ahead of the publication of Barnardo paper (August 2000). And while Thomas' allegations may be true for "many proteins", this was clearly not true for MHC Class II monomers as described by Frayser and Arimilli.

Regarding the Frayser and Arimilli references, the Examiner appears to have relied upon their respective characterizations of prior work but did not recognize that each successfully demonstrated expression of properly folded MHC Class II molecules. For example, on p. 105, col. 2, Frayser characterizes certain prior work as follows:

> Previous efforts to prepare recombinant complexes of class II MHC proteins with single, defined peptides (8-12) or empty, peptide-free molecules (9, 10, 13, 14) have met with limited success.

However, as to their own work, Frayser states:

> Genes coding for the extracellular domains of the human class II MHC protein HLA-DR1 α and β sub-units were used for expression in E. coli. The DRα and DRβ subunits were expressed in good yields by T7-driven expression (Fig. 1). (p. 108, col. 2)
>
> Under appropriate conditions, refolding *in vitro* of HLA-DR1 subunites produced in *E. coli* inclusion bodies proceeds in a relatively high yield in the presence or absence of peptide. The isolated protein is free of aggregates and monomeric α or β subunits and has adopted the native fold as judged by circular dichroism. (p. 112, DISCUSSION)
>
> We conclude that the recombinant DR1 has adopted to native fold. We have folded DR1 in the absence of peptide and isolated a soluble, peptide-free αβ-heterodimer. The empty DR1 can bind antigenic peptide. (p. 105, Abstract)

Thus, Frayser concludes that recombinant MHC Class II monomers were successfully prepared.

Similarly, Arimilli characterizes prior work as having met some obstacles, but characterizes their own work as follows:

> In this report, we describe the refolding of E. coli-expressed recombinant human a and b chains lacking the transmembrane regions followed by reconstitution of biologically active HLA DR2. (p. 972)
>
> In conclusion, results presented here demonstrate the formation of functionally active HLA DR2 heterodimeric complexes containing antigenic epitopes.

> The yield of such complexes is approximately 800-fold higher than the native DR2 molecules. (p. 976)

As for Frayser, Arimilli also demonstrates the successful preparation of recombinant MHC Class II monomers.

It is clear that the Frayser and Arimilli references do not support the Examiner's conclusion that "one of ordinary skill in the art would have a low level of predictability in making MHC class II monomers." And the Examiner's mere conclusion that "random experimentation is undue" is improper, especially as it is based on incorrect characterizations of the prior art. It is therefore respectfully requested that these rejections be withdrawn.

B. Rejections Under 35 U.S.C. § 102(a)

Claims 1-7, 13, 16 and 17 stand rejected under 35 U.S.C. 102(a) as being anticipated by Barnardo et al. (Detection of HLA antibodies using single recombinant HLA alleles, Human Immunology, Abstracts 1999, Vol. 60, Suppl. 2). Applicants respectfully disagree and traverse these rejections as indicated below.

The Examiner alleges that the abstract is prior art because the reference includes authors other than the inventors named on the present application. However, as stated in point 2 of Dr. Bunce's declaration, Graham Ogg merely provided HLA class I monomers. As stated at point 3 of Dr. Bunce's declaration, Olivia Shaw merely carried out technical work under the direction of Andrea Harmer. As stated at point 4 of Dr. Bunce's declaration, neither Graham Ogg nor Olivia Shaw made any inventive contribution to the methods claimed in this application. As such, this reference is not "by others", and is not prior art. Accordingly, then, this rejection is improper and its withdrawal is respectfully requested.

C. Rejections Under 35 U.S.C. § 102(a)

Claims 1-7, 13, 16 and 17 stand rejected under 35 U.S.C. 102(a) as being anticipated by Barnardo et al. (Detection of HLA antibodies using single recombinant HLA alleles, Human Immunology, Abstracts 1999, Vol. 60, No. Suppl. 1, pp. S1). Applicants respectfully disagree and traverse these rejections as indicated below.

The Examiner alleges that the abstract is prior art because the reference includes authors other than the inventors named on the present application. However, as stated in point 2 of Dr. Bunce's declaration, Graham Ogg merely provided HLA class I monomers. As stated at point 4 of Dr. Bunce's declaration, Graham did not make any inventive contribution to the methods claimed in this application. As such, this reference is not "by others", and is not prior art. Accordingly, then, this rejection is improper and its withdrawal is respectfully requested.

D. Rejections Under 35 U.S.C. § 103(a)

1. Rejection of claims 1-7 and 11-17 over Lee, Chang, and Walter.

Claims 1-7 and 11-17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lee et al. (U.S. Pat. No. 5,948,627) in view of Chang et al. (U.S. Pat. No. 5,270,169) and further in view of Walter et al. (Int. Immunol., Vol. 9, No. 3, pp. 451-459, 1997). Applicants respectfully disagree and traverse these rejections as indicated below.

The Examiner alleges that the pending claims are obvious in view of the cited references because:

1) Lee discloses a method for detection of HLA antibodies by adding serum to microbeads containing immobilized HLA antigens, and then detection of any bound anti-HLA antibodies using a labeled ligand, although Lee is not alleged to disclose the use of recombinant MHC or HLA molecules;
2) Chang discloses that "it is known in the art that synthetic HLA antigens which mimic the antigenic reactivity of HLA epitopes are equivalent to HLA antigens for the detection of specific antibodies in a biological sample"; and,
3) Walter shows that recombinant HLA antigens can be used to detect allele specific antibodies and that the recombinant complexes contain native epitopes, consistent with the presence of correctly folded molecular complexes.

Thus, the Examiner alleges that it would have been obvious "to substitute a recombinant HLA antigen and the corresponding reagents as taught by Walter et al into the modified method of Lee et al because Chang et al discloses that it is known in the art of detecting

HLA antibodies that a synthetic HLA antigen can be substituted as an equivalent reagent for HLA antigens for the purpose of detecting HLA antibodies and Walter shows that recombinant HLA antigens can be used to detect allele specific antibodies and that the recombinant complexes contain native epitopes, consistent with the presence of correctly folded molecular complexes." Applicants respectfully disagree with the Examiner's conclusions.

The pending independent claims (1, 2 and 20) of this application relate to methods (claims 1 and 2) or kits (claim 20) for detecting anti-MHC antibodies (such as anti-HLA antibodies) in a body fluid sample. Immobilized recombinant MHC molecules (such as recombinant HLA molecules) that "each bind to a different allele specific MHC antibody" are used to detect the binding of antibodies specific to a particular MHC molecule. Thus, the assay indicates to which particular type of MHC molecule an antibody in the body fluid sample binds. This is neither demonstrated nor suggested by any of the cited references, and cannot be properly derived from a combination thereof.

Lee and Chang do not discloses the use of recombinant MHC class I or class II molecules, and do not show the skilled artisan how to detect antibodies with specificity for a particular recombinant MHC molecule. Lee discloses the attachment of multiple types of HLA molecules isolated from EBV transformed lymphocyte cell lines to beads and an assay to detect antibodies reactive therewith. Each of Lee's microbeads contain at least two different types of cell-derived, non-recombinant HLA molecules (e.g., Bead No. 25 includes A30 and B42). Chang discloses the detection of non-recombinant, soluble HLA molecule / anti-HLA antibody complexes using C1q proteins attached to microtiter plates. Chang uses "the culture supernatant of a lymphoblastoid cell line [as] a source of soluble HLA antigen". Chang does not specify which HLA antigens are being utilized in the assays. One of skill in the art would not understand Chang to be using a particular HLA antigen but rather whichever HLA molecules are expressed by the undefined "lymphoblastoid cell line". Chang states generally, but provides no examples whatsoever relating to the "synthetic HLA antigens" referred to by the Examiner. Neither of these references discloses the claimed method or kits of the pending claims.

The Examiner alleges that Walter satisfies the deficiencies of Lee and Change by showing "recombinant HLA molecules can be used to detect antibodies in a sample."

However, this is not disclosed by Walter. At page 452 (cited by the Examiner), Walter discloses the covalent attachment of anti-β2-microglobulin and anti-HLA-A2/B17 monoclonal antibodies to cells which were then exposed to HLA-A2 peptide complexes. The binding of such complexes to the attached monoclonal antibody was shown using a FITC-conjugated anti-HLA-A,-B,-C monoclonal antibody (mAb BB7.7-FITC conjugate; Walter, Fig. 2). Walter does not show the detection of monoclonal PA2.1 antibodies from a body fluid sample (or kit for doing the same); rather, all that is shown is the "[a]dsorption of HLA-A2 peptide complexes to mAb-coated cells" (Walter, p. 453). On page 456 (cited by the Examiner), Walter demonstrates that recombinant HLA-peptide complexes can be used to stimulate T cells. The closest Walter comes to detecting anti-MHC antibodies in a "body fluid sample" is the polyclonal antisera described in Fig. 4 but this polyclonal antisera is against heavy chain and is not allele-specific. Detection of allele-specific antibodies in a body fluid sample as instantly claimed is simply not taught or suggested by Walter. As such, Walter does nothing to satisfy the deficiencies of Lee and Chang.

For these reasons, Applicants believe that the Examiner has not established a *prima facie* case of obviousness of the pending claims and therefore respectfully request withdrawal of this rejection.

2. Rejection of claim 12 over either Barnardo reference in view of Pouletti.

Claim 12 stands rejected under 35 U.S.C. § 103(a) over Barnardo (Supplement 2) or Barnardo (Suppl. 1, pp. S1) in view of Pouletti et al. (U.S. Pat. No. 5,292,641). Applicants respectfully disagree and traverse these rejections as indicated below.

It is only "where an inventor publishes more than one year before filing [that] he or she forecloses obtaining a patent on an invention that would have been obvious from the publication…." In re O'Farrell, 853 F.2d 894 (Fed. Cir. 1988). Applicants' priority date of March 17, 2000 is prior to the expiration of one year from the earliest publication date of either Barnardo reference. As neither Barnardo reference is available as prior art, this rejection is improper and its withdrawal is respectfully requested.

3. Rejection of claims 14 and 15 over Barnardo (Supplement 2) or Barnardo (Suppl. 1, pp. S1) in view of Baserga et al. (U.S. Pat. No. 6,218,363).

Claims 14 and 15 stand rejected under 35 U.S.C. § 103(a) over Barnardo (Supplement 2) or Barnardo (Suppl. 1, pp. S1) in view of Baserga et al. (U.S. Pat. No. 6,218,363). Applicants respectfully disagree and traverse these rejections as indicated below.

Applicants have previously shown that the Barnardo references are not prior art under 35 U.S.C. § 103. As neither Barnardo reference is available as prior art and the Baserga reference does not stand alone, this rejection is improper and its withdrawal is respectfully requested.

4. Rejection of claims 20, 22, 24-27 and 29 over either Barnardo reference and Boguslaski.

Claims 20, 22, 24-27 and 29 stand rejected under 35 U.S.C. § 103(a) over Barnardo (Supplement 2) or Barnardo (Suppl. 1, pp. S1) in view of Boguslaski et al. (U.S. Pat. No. 5,420,016). Applicants respectfully disagree and traverse these rejections as indicated below.

Applicants have previously shown that the Barnardo references are not prior art under 35 U.S.C. § 103. As neither Barnardo reference is available as prior art and the Boguslaski reference does not stand alone, this rejection is improper and its withdrawal is respectfully requested.

5. Rejection of claims 20, 22, 24 and 29 over Lee, Chang, Walter, and Boguslaski.

Claims 20, 22, 24 and 29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lee et al. (U.S. Pat. No. 5,948,627) in view of Chang et al. (U.S. Pat. No. 5,270,169) and Walter et al. (Int. Immunol., Vol. 9, No. 3, pp. 451-459, 1997), and further in view of Boguslaski et al. (5,420,016). Applicants respectfully disagree and traverse these rejections as indicated below.

As described above, Applicants respectfully maintain that the Examiner has not established a *prima facie* case of obviousness of the pending claims with respect to Lee, Change and Walter. Applicants further maintain that Boguslaski does nothing to satisfy

the deficiencies thereof. Accordingly, Applicants respectfully request withdrawal of this rejection.

6. Rejection of claims 25-27 over Lee, Chang, Walter, Boguslaski and Luxemborg.

Claims 25-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lee et al. (U.S. Pat. No. 5,948,627) in view of Chang et al. (U.S. Pat. No. 5,270,169), Walter et al. (Int. Immunol., Vol. 9, No. 3, pp. 451-459, 1997), and Boguslaski et al. (5,420,016), and further in view of Luxemborg et al. (U.S. Pub. No. 2004/0137617). Applicants respectfully disagree and traverse these rejections as indicated below.

As described above, Applicants respectfully maintain that the Examiner has not established a *prima facie* case of obviousness of the pending claims with respect to Lee, Change and Walter. Applicants further maintain that neither Boguslaski nor Luxemborg do anything to satisfy the deficiencies thereof. Accordingly, Applicants respectfully request withdrawal of this rejection.

Conclusion

Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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